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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/552,881

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Simone Charlotte Vonwiller

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KNOBBE MARTENS OLSON & BEAR LLP  
2040 MAIN STREET  
FOURTEENTH FLOOR  
IRVINE, CA 92614

EXAMINER

PALENIK, JEFFREY T

ART UNIT

PAPER NUMBER

1615

NOTIFICATION DATE

DELIVERY MODE

04/22/2009

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com

eOAPilot@kmob.com

<b>Office Action Summary</b>	<b>Application No.</b> 10/552,881	<b>Applicant(s)</b> VONWILLER ET AL.	
	<b>Examiner</b> Jeffrey T. Palenik	<b>Art Unit</b> 1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 26 November 2008.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 36-69 is/are pending in the application.
- 4a) Of the above claim(s) 51-66 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 36-50 and 66-69 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 26 November 2008 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

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### **DETAILED ACTION**

Receipt is acknowledged of Applicant's amendments and remarks filed 26 November 2008. The Examiner acknowledges the following:

Claims 1-35 were cancelled prior to the previous Office Action.

Claims 51-66, while still pending, are presently withdrawn from consideration.

Claims 67-69 have been added. Support for the claims is found in Applicant's originally submitted claims.

Claims 36, 38 and 45-47 have been amended. Claim 36 has been amended such that the "optional" washing step has been removed, the remaining method steps have been re-lettered and minor edits were made for clarity. Claim 38 was amended to clarify the recited polysaccharide Markush group. claims 45 and 46 were amended editorially. Claim 47 was amended to depend from newly added claim 67, which recites the washing step (i.e. not optional) which was amended out of claim 36.

Thus, claims 36-50 and 67-69 now represent all claims currently under consideration.

### **INFORMATION DISCLOSURE STATEMENT**

No new Information Disclosure Statements (IDS) have been submitted for consideration.

### **WITHDRAWN OBJECTIONS/REJECTIONS**

#### Objection to the Drawings

Applicants' newly submitted drawings have been considered and found acceptable. Thus, said objection has been **withdrawn**.

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Rejection under 35 USC 112

Applicants' amendment to claim 36, as discussed above, renders moot the indefiniteness rejection, under 35 USC 112, second paragraph. Thus, said rejection has been **withdrawn**.

Applicants' amendment to claim 38, as discussed above, renders moot the indefiniteness rejection, under 35 USC 112, second paragraph. Thus, said rejection has been **withdrawn**.

**MAINTAINED REJECTIONS**

The following rejections are maintained from the previous Office Correspondence dated 5 September 2008 since the art which was previously cited continues to read on the amended limitations.

**CLAIM REJECTIONS - 35 USC § 102**

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 36-41, 46 and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhao (WO 00/46253).

The instant claims are directed to a process for producing a cross-linked gel comprising mixing (e.g. contacting) an alkaline-based polysaccharide medium with an epoxide cross-linking agent via ether bonds, drying said gel without removing the ether bonds, washing the gel with a water miscible solvent and neutralizing said gel using an acidic medium (claim 1). The

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polysaccharide is further recited as hyaluronic acid or (HA) (claims 37-39). The epoxide is further recited as butanediol diglycidyl ether (claims 40 and 41). The mixing, drying and washing steps are recited as being performed under alkaline conditions with acetone (claims 46 and 47).

Zhao teaches a method for producing a cross-linked gel wherein an alkaline solution of hyaluronic acid in sodium hydroxide is mixed with varied volumes of the multifunctional epoxide 1,2,7,8,-diepoxyoctane, drying said mixture into a gel formation, purifying (e.g. washing) the dried gel using acetone/water, acetone and isopropyl alcohol (IPA), and neutralizing said gel in an acidic medium of acetone/hydrochloric acid at pH 5 (Example 6 and claim 1). Claim 4 teaches additional cross-linking agents such as butanediol diglycidyl ether.

#### **RESPONSE TO ARGUMENTS**

Applicants' arguments with regard to the rejection of claims 36-41, 46 and 47, under 35 USC 102(b) as being anticipated by Zhao et al. (WO 00/46253), have been fully considered, but are not persuasive.

Applicants allege that Zhao teaches away from the method recited in the instant claim 36, particularly since Zhao teaches that the hyaluronic acid (HA)/epoxide mixture is allowed to sit for a period of 24 hours prior to the drying step, which occurs over an additional 48 hours. Applicants further allege that Zhao teaches away from the instantly claimed invention on the grounds that Zhao teaches the formation of multiple types of cross-linkages, whereas the instant claims are directed to the formation of a single type of cross-linkage [*emphases added*].

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In response to Applicants' argument that the references fail to show certain features of the instantly claimed invention, it is noted that the features upon which Applicants rely (i.e., 72-hour period from mix to dry; single versus multiple cross-linkage formation) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Thus, for these reasons, Applicants' arguments are found unpersuasive. The above rejection is hereby maintained. The above rejection is hereby maintained as well as extended to new claims 67-69.

### **CLAIM REJECTIONS - 35 USC § 103**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

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Claims 36-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhao (WO 00/46253) in view of Mälson (WO 87/07898).

The instant claims are directed to a process for producing a cross-linked hyaluronic gel, as discussed above. Various conditions under which the procedure is performed such as pH (claim 42), component concentration (claim 43), and reaction and drying temperatures (claims 44 and 45) are recited. Claims 48 and 49 recite step (d.) as further comprising freeze-drying or lyophilizing the produced gel and reconstituting it in phosphate buffered saline (PBS). The term “reconstituting”, viewed in its broadest and most reasonable terms, is interpreted by the Examiner as reciting “restoration to a former condition by adding water”. In the case of claim 49, this is interpreted as restoration using a water-based medium such as PBS. Claim 50 recites the gel as further comprising a biologically active substance.

The teachings to Zhao are discussed above. Zhao further teaches that the starting solution for an alkaline solution is preferably at a pH of 10 or more and that the reaction may effected at a temperature in the range of 15 to 50°C (pg. 9, line 27 to pg. 10, line 4). Example 6 further teaches that the starting solution is a 2.5% solution of hyaluronic acid in sodium hydroxide (HA/NaOH) which is mixed with varying amounts of epoxide. Tables 1-3 teach varying “feeding ratios” of HA to the cross-linking compound. Drying of the gel at a temperature of at least about 35°C (i.e. in a 37°C oven) is taught (Examples 1-3). Restoration of the gel product from a dried film or sheet format by immersing it in PBS is taught (pg. 11, lines 11-15). Incorporation of a biologically active substance into the gel is taught (claims 1, 15, 22 and 23).

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Freeze drying as a means for drying the gel to a film or sheet format is not expressly taught by Zhao. Nor is it expressly taught that the gel is dried under a vacuum.

Mälson teaches the preparation of a cross-linked polymerized gel product (e.g. an insoluble, porous spongy material) wherein sodium hyaluronate or hyaluronic acid is dissolved into sodium hydroxide, mixed with 0.15 wt./volume % butanediol diglycidyl ether (BDDE), washed (e.g. dialysed) with water and then dried to form the film under acidic conditions (Example 1 and claims 1-7). Example 9 expressly teaches drying the formulation using freeze-drying. Example 19 teaches incorporation of Vitamin A as a biologically active substance which is controllably released from said gel by immersion into a volume of buffer. "Physiological saline" such as PBS is taught as being used to swell or restore the gels (pg. 9, second paragraph; pg. 8, bottom paragraph).

Mälson does not expressly teach the steps of the method in order or all of the specific reaction conditions as instantly claimed (e.g. vacuum drying).

In view of the combined teachings of the prior art, one of ordinary skill in the art, at the time of the invention, would have been motivated to use the instantly claimed method in order to prepare a hyaluronic acid and epoxide cross-linked polymerized gel. Such would have been obvious in the absence of evidence to the contrary since Zhao expressly teaches the procedure with the exception of certain particular claimed parameters (i.e. compositional epoxide percentage, vacuum drying, or freeze-drying). With the exception of certain adjustable parameters, the art taught by Mälson overlaps in its teaching of method steps (e.g. alkaline



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starting solutions mixed with epoxides) and components (e.g. hyaluronic acid and butanediol diglycidyl ether) with Zhao, both of which can be incorporated to arrive at the instant method claims. Lyophilization, while not taught by Zhao, is a method which is well known in the art by the skilled artisan as a means for preserving gels as dehydrated films. Furthermore, though neither of the practiced inventions expressly teaches using a drying the gel preparations at higher temperatures using a vacuum drying oven, one of ordinary skill in the art would be well motivated to employ such an oven if for no other reason than to minimize the risk of particulate contamination in the dried gel product.

Therefore, a person of ordinary skill in the art would have a reasonable expectation of success in modifying the gel-producing method practiced by Zhao with the freeze-drying gel preparation step taught by Mälson since the combined teachings disclose the instantly claimed method for producing a biologically active cross-linked gel composition. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

While neither Zhao nor Mälson teach the instantly claimed pH, temperature and percentage ranges, as instantly claimed by Applicants, Zhao offers a broader teaching of said parameters in the practiced Examples and Tables, as discussed above. Since the values and formats of each parameter with respect to the claimed composition are adjustable, it follows that each is a result-effective parameter that a person having ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. As evidenced by the combination of the two teachings, it would have been customary for an artisan of ordinary skill, for example, to adjust the amount of

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multifunctional epoxide-based cross-linking agent, in order to achieve the desired gel composition. Thus, absent some demonstration of unexpected results from the claimed parameters, optimization of any of these parameters would have been obvious at the time of Applicants' invention.

#### RESPONSE TO ARGUMENTS

Applicants' arguments with regard to the rejection of claims 36-50 under 35 USC 103(a) over the combined teachings of Zhao et al. and Mälson et al. have been fully considered but they are not persuasive.

Applicants allege that the combined teachings provided by the references teach away from the instantly claimed invention on the grounds of the types/quantity of cross-linkages formed by Zhao (e.g. single versus multiple), as discussed above. Applicants further discuss that the teachings of Mälson describe a cross-linking process in which excess cross-linker is removed prior to drying, which is thus allegedly contrasted to the instantly claimed limitation whereby drying takes place without substantially removing epoxide [emphases added]. Applicants further attest to the presence of excess cross-linker being present during the drying step.

In response to Applicants' argument that the references fail to show certain features of the instantly claimed invention, it is noted that the features upon which Applicants rely (i.e., single versus multiple cross-linkage formation; presence of excess cross-linker during any step) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

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Furthermore, the Examiner respectfully disagrees with Applicants' remarks regarding the presence excess cross-linker. The instantly claimed method step (b.) recites that substantially no epoxide is removed from the gel prep during the drying step. Claim 1 of Mälson recites that the reagents are mixed, that the excess bi- or polyfunctional reagent (e.g. the epoxide cross-linker) is removed and then in a second step, the gel prep is dried. Thus Mälson does not teach or suggest the removal of the epoxide cross-linker during the drying step, but rather prior to the drying step. As such, the removal of excess cross-linker as taught by Mälson, though not a limitation of the rejected claims, does read on the instantly claimed method.

For these reasons, Applicants' arguments are found unpersuasive. Said rejection is therefore maintained. The above rejection is hereby maintained as well as extended to new claims 67-69.

All claims under consideration remain rejected; no claims are allowed.

### **CONCLUSION**

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

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CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

#### **CORRESPONDENCE**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966. The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey T. Palenik/  
Examiner, Art Unit 1615

/MP WOODWARD/  
Supervisory Patent Examiner, Art Unit 1615